Effects of Magnetic Fields on Biological Systems

An Overview

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Introduction

Magnetism is a fundamental part of life. It plays a role in bird migration and fish navigation, among other phenomena. The earth's magnetism enables navigating with a compass. Magnetism exists whenever there is electric current; electricity provides a convenient means for creating magnetic fields for other uses, for example, in medicine.

Magnetic fields have been used for various medical purposes since 2500 BC. Animals and bacteria sense the earth's magnetic field. The search for how magnetic fields produce biological effects has driven exploration in a multitude of experimental systems, clinical studies, and the clinical use of FDA-approved devices. Various aspects of the effects of applied magnetic fields are understood, while others remain the subject of research. Even so, magnetic fields are used successfully for many medical applications, e.g., magnetic resonance imaging, to speed bone fracture repair, to increase the rate of wound healing, to decrease pain and to treat depression and obsessive-compulsive disorder.

Magnetism

Magnetic fields arise from ferromagnetic materials, such as iron and nickel, or from electric current. For example, the earth's magnetic field is generated by the molten iron alloy in the outer core. Medical applications take advantage of the interconnection between electricity and magnetism.

Current in a wire produces a magnetic field (Faraday, 1839). The properties of the field depend on the properties of the current. If the current's amplitude does not change, it produces what is referred to as a static magnetic field. A current with changing amplitude produces an oscillating magnetic field. Both types of field have played a role in the biological investigations of magnetic field effects.

Proposed Mechanisms of Action

Several ideas have driven the experimental search for the mechanism of the biological effects of magnetic fields.

One fundamental property of an oscillating magnetic field is that it can induce current flow in a conducting medium. This fundamental phenomenon of a magnetic field gives rise to the theory that a field-induced current may alter the behavior of a cell's membrane channel. For example, calcium or sodium ions can move across the cell membrane, and such a change may cause a nerve to fire. A current might alter the movement of calcium ions into the cell, which activates several pathways that influence the cell's physiology.

Another possible mechanism is that a magnetic field changes the binding properties of specific proteins and alters the properties within a cell, such as that of a protein known as calmodulin, which is regulated by calcium binding.

A third theory regarding the effect of magnetic fields is that they alter nitric oxide and reactive oxygen species. Nitric oxide is a regulator of several important regulatory pathways in cells. Alterations in reactive oxygen species change cell metabolism.

Unequivocal identification of the precise mechanism that elicits a specific outcome in a cell, tissue or patient is the subject of ongoing research.

Influences of the Earth's Magnetic Field

The Earth generates a magnetic field. Life on this planet has evolved surrounded by the geomagnetic environment generated by the Earth (Lohmann, 2010). Animals as diverse as bats, worms, birds, sea turtles and lobsters can sense changes in the local magnetic environment (Clites and Pierce, 2017; Lohmann, 2010) and can use them for navigation (Heyers et al., 2017; Vidal-Gadea et al., 2015) and foraging (Tian et al., 2019).

The mechanism by which the Earth's magnetic field is sensed has not been unambiguously determined (Clites and Pierce, 2017; Lohmann, 2010). In some organisms, specialized cells contain iron particles that may act as sensors. In other cases, no specialized protein or cell organelles have been identified to detect magnetic fields.

Device-Generated Magnetic Fields

Magnetic fields have been shown to alter the analgesic effects of opioids, produce analgesic responses, stimulate bone growth, reduce tissue swelling, and promote wound healing in both animal models and humans. Magnetic fields that enhance bone growth and aid in wound healing have been in clinical use for at least 40 years (Assiotis et al., 2012). Pain reduction has been observed in studies of breast reconstruction (Rohde et al., 2015)and breast reduction (Taylor et al., 2015), post-cesarean operative recovery (Alvarez, 2017), and osteoarthritis (Nelson et al., 2013). Analgesic and opioid use and edema were also reduced in breast reduction, breast reconstruction and post-caesarean patients.   Devices generating magnetic fields are effective treating major depression and obsessive compulsive disorder, and such devices are recommended for treating acute phase of depression in patients who are resistant and intolerant of other therapeutic options (Perera et al., 2016).

In concert with the clinical development of magnetic field use, researchers have attempted to define the underlying biological effects that lead to the field's therapeutic effects and to relate them to one or more of the underlying theories of magnetic field function. This work has included isolated protein systems, cells grown in culture, and organisms ranging from nematodes to mammals, as well as numerical modeling of the functions of the cell. Examples of these types of investigations are discussed next.

Changes in the expression of heat shock protein (HSP) have been detected in planaria (Goodman et al., 2009; Tessaro and Persinger, 2013) and *C. elegans* (Junkersdorf et al., 2000; Miyakawa et al., 2001).

Pre-treatment of MS-1 cells with a magnetic field increased the heat shock proteins HSP70 and HSP90 (Delle Monache et al., 2013). A similar increase in HSPs in HL-60 (Pipkin et al., 1999), chicken embryos and SH-SY5Y neuroblastoma cells (Osera et al., 2011) have been reported.

Magnetic fields alter the behavior of the epidermal growth factor receptor (EGFR), an important regulator of cell growth. This receptor, when exposed to a magnetic field, forms clusters in the membrane, which leads to phosphorylation of the receptor and to activation of one of the receptor targets, ras. These changes reflect what occurs when epidermal growth factor (EGF) binds to EGFR and indicate that the magnetic field activated the receptor in the absence of its natural activator EGF (Ke et al., 2008; Sun et al., 2018; Sun et al., 2008; Sun et al., 2013; Wang et al., 2016; Wu et al., 2014). Proliferation and cell migration are affected by magnetic fields (Delle Monache et al., 2013).

Mice injected with a transformed cell line formed smaller tumors when treated with magnetic fields (Delle Monache et al., 2013). Additional studies in models of cancer demonstrate effects of magnetic fields (Novikov et al., 2009; Novoselova et al., 2019) (Buckner et al., 2015, 2017) (Nie et al., 2013) (Xu et al., 2017) (Verginadis et al., 2019).

Though a definitive answer to the question of how these fields exert their effects is not available, evidence that magnetic fields have beneficial effects in therapeutics is abundant.

Ultra-Low Radio Frequency Energy (*ul*RFE®)

EMulate Therapeutics, Inc. (www.emulatetx.com) has developed a patented, proprietary technology using an oscillating magnetic field to produce therapeutic effects. EMulate's Voyager device produces a broadband, multifrequency field, with frequencies up to roughly 22 kHz, that is obtained from the recordings of selected molecules. While the details of the mechanism of action are not known, recordings are hypothesized to capture features of the recorded molecule that alter cellular behavior. The EMulate Voyager device is currently in clinical testing for patients with terminal brain cancer, using a field derived from the molecule paclitaxel.

Examples of biologic activity with *ul*RFE fields include experiments conducted to demonstrate the specificity and cellular effects of a specific *ul*RFE targeting epidermal growth factor receptor, EGFR, on glioblastoma cell line U-87 MG. At 48 and 72 hrs, EGFR inhibition by the ulRFE reduced the level of EGFR protein by 27% and 73%, respectively. These data indicate that *ul*RFE can inhibit gene expression at the transcriptional and protein levels, similar to what is observed with physical small interfering RNA (siRNA) inhibition (Ulasov et al, 2017). Specific

EGFR knockdown effect was detected in U-87 MG cells treated with *ul*RFE using an 80 gene PCR-based array.

Additionally, experiments conducted in *Chlamydomonas reinhardtii* with a *ul*RFE siRNA against MAA7 (tryptophan synthase beta) showed a decrease in mRNA levels for MAA7. In cells exposed to the *ul*RFE signal, an increase in cell growth was observed as compared to no *ul*RFE signal (Butters, 2017).

Voyager has been tested in over 400 dogs (pets) with naturally occurring malignancies by Dr. Greg Ogilvie (Angel Care Cancer Center, LA). Interim review of the first 200 pets observed partial responses and complete responses in over 20 different tumor types. No clinically important or significant toxicities (Grade 3 or 4) were observed.

An early feasibility study (the equivalent of a FDA IND Phase 1 / 2 study) results of the EMulate Voyager device in patients with recurrent glioblastoma are encouraging and have shown a median overall survival (OS) of 7 months in a Voyager-alone arm and 10 months in the Voyager plus standard of care arm (Barkhoudarian et al, 2020)). The median progression free survival (PFS) in this study was 10 weeks for Voyager alone and 16 weeks for Voyager plus standard of care. For comparison, the median OS for “active drugs” in this disease is 7.2 months, meaning Voyager appears to have a similar effect to chemotherapy for this patient population in this study, without patients taking chemo. When Voyager is added to “active drugs” OS improves to 10 months in this cohort of patients. PFS for historically active therapies is 9.1 weeks (Stupp et al, 2012). These data suggest that the Voyager is safe and feasible for the treatment of recurrent GBM. A study in newly diagnosed glioblastoma is ongoing with the Voyager device with encouraging results.

Additional data were recently presented demonstrating behavioral changes in mice that were exposed to fields derived from chemistries intended to either stimulate or suppress behavior. Under controlled and blinded conditions, an independent evaluator noted the mice reacting consistently to the magnetic field they were exposed to, as if they had ingested the correlating compound (Figueroa et al, 2019).

Summary

Multiple studies in a variety of systems indicate that magnetic fields can alter biological function. Therapeutically useful devices are used presently in clinical practice, both in human and veterinary medicine. Treatment for bone growth, wound healing, arthritis pain and depression are among the clinical uses. Research aims to understand better how these fields exert their effects to further enable new and exciting therapeutic options for many diseases.

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